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BRAIN MECHANISMS UNDERLYING INDIVIDUAL DIFFERENCES

IN REACTION TO STRESS: AN ANIMAL MODEL

FINAL REPORT

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The cat and rat were investigated as animal models for the correlation of individual behavior with a readily obtainable electrophysiological measure, viz. augmenting/reducing of the visual evoked potential (VEP). The VEP in cats was found to be an identifiable individual signature, stable over periods of more than one year. The VEP in response to an intensity series of light flashes at a medium range of intensities was reliable over time and showed significant individual differences in response to the more intense stimuli. Some cats showed increasing VEP amplitudes to intense stimulation (continued)

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20. ABSTRACT

(augmenters), while others showed cortical inhibition, reducing the amplitude of the VEP to more intense stimuli (reducers). Augmenter cats were more exploratory and active in a behavioral chamber, and when confronted with a variety of novel and/or aversive stimuli were more reactive and responsive. This behavioral difference predicted task performance in an operant conditioning chamber. The augmenter cats were more reactive and were not as effective in exerting inhibitory control on behavior as were the reducers. Reducer cats learned a bar press inhibitory task more quickly, were less distracted by loud noise bursts and were able to tolerate more difficult tasks than the augmenter cats.

In the rat, evidence was obtained that augmenting/reducing as measured by the VEP afterdischarge amplitude was related to frontal pole control of arousal mechanisms. Work on the rat is continuing to see if this species can serve as a simple animal model for augmenting/reducing.

STATEMENT OF PROBLEM

In human studies, the change in amplitude of the visual evoked potential (VEP) in response to an intensity series of light flashes shows individual differences which are very stable over short periods and moderately stable over longer periods (Buchsbaum 1971; Birchall & Claridge 1979; Soskis & Shagass 1974). Those individuals whose VEP amplitudes increase with intensity are called augmenters, while those whose amplitudes decrease over the same range of intensities are termed reducers. Augmenting/reducing has been found to be correlated with clinical psychopathology (Buchsbaum et al. 1971; Schooler et al. 1976; Gershon & Buchsbaum 1977; Buchsbaum et al. 1977), personality scales of extraversion/introversion (Haier 1984) and sensation seeking (Zuckerman et al. 1974, 1980; Lukas 1981a), and with pain tolerance (Buchsbaum 1978; Buchsbaum & Haier 1983). This readily obtained psychophysiological index may provide a measure of individual differences in response to high levels of sensory stimulation which would be valuable in screening personnel for performance during stressful task assignments. However, there is still controversy as to the generality of the augmenting/reducing phenomenon (Lukas 1981b; Connolly & Gruzelier 1982), its validity over modalities (Raine et al. 1981), the personality characteristics with which it is correlated (Soskis & Shagass 1974, Andress & Church 1980), and the neurophysiological basis for the phenomenon.

An animal model of augmenting/reducing would make it possible to resolve some of this controversy by repeated testing of evoked potentials and behavior to clarify the generality of the phenomenon, and by invasive studies to explore the neurophysiological mechanisms. Two previous studies of augmenting/reducing in the cat (Hall et al. 1970, Lukas & Siegel 1977) indicated that the phenomenon does exist in this species and is correlated with behavioral reactions but both studies were based on only one or two series of VEP determinations. Cats whose VEP amplitudes increased with intensity (augmenters) were found to be more reactive and responsive to novel and/or frightening stimuli, while reducers tended to ignore the stimuli or "freeze" in response to alarming stimuli.

The research described in this final report was designed to 1) investigate the stability and reliability over time of the change in VEPs to an intensity series of light flashes in

cats and rats, and 2) correlate this measure with behavior. Cat behavior was analyzed in two situations. As in previous studies spontaneous behavioral reactions to a variety of stressful and/or novel stimuli such as loud noises, taped sounds of birds calling, cats fighting, etc. were observed and rated. While these behaviors are indicative of the cat's individual temperament and emotional reactivity, they are not necessarily related to its coping abilities in a task oriented situation. Therefore performance in a fixed interval or differential reinforcement of low rate of response (DRL) bar press paradigm was also measured and correlated with the VEP augmenting/reducing. Stressors were introduced during the task in the form of random bursts of loud noise or increasing task difficulty. In rats the primary components of the VEP and the photically evoked after discharge were measured and correlated with arousal and activity in 2 experimental situations 1) after frontal lobe lesions and 2) in complex versus simple novel environments. Following these experiments a mirror box was constructed and the reliability of VEP measures in the awake, unrestrained rat studied.

RESULTS: CAT STUDIES

1. In the first experiment four cats were prepared with deep electrodes in optic tract and optic radiations and recording screws over visual cortex. Centrally evoked visual potentials were recorded during the cats' behavioral responses to novel and/or stressful stimuli. The 6 stimuli in order of presentation were: taped sounds of 1) birds chirping, 2) dogs barking, and 3) cats fighting; 4) high pressure oxygen whipping a hose; 5) a mechanical dog; and 6) 20 sec. bursts of a loud noise (100 dB). Ratings were made on 6 behavioral measures (orientation, emotionality, tension, recovery, approach and withdrawal) for the cat's reaction to three presentations of each stimulus. The VEP decrease for all cats was greatest during presentation of the most alarming stimuli. Those cats whose VEP amplitudes to peripheral light flash increased with intensity (augmenters) showed the greatest change in cortical functioning. Correlations of augmenting/reducing with electrophysiological and behavioral responses to stressful stimuli were promising but not significant.

2. Repeated sessions revealed a large variability in the VEP amplitudes and slopes. One source of variability was found to be the use of the frontal sinus as the location for

the indifferent recording screw. Seven cats were studied in multiple sessions, recording the electroretinogram as well as visual evoked potential differentially against either a frontal sinus screw or inert neck muscle electrode as indifferent. The frontal sinus screw electrode was found to be recording a volume conducted retinal potential from the eye, which varied with light adaptation, rate of presentation and intensity of the stimulus. This study was presented at the annual meeting of the Society for Neuroscience (Siegel & Saxton 1982)and later published (Saxton & Siegel 1983, abstract and paper appended). All succeeding studies used a fine needle inserted into the inert neck muscle as an electrode indifferent.

3. The effect of the intensity range of light flash on the augmenting/reducing response of individual cats was studied using three intensity ranges one log unit apart. Each cat responded to the intensity series of light flashes with characteristic VEPs which were stable in shape over Flaxedil sessions a month apart as well as between intensity series on the same day. However, quantitative measurement of baseline to peak or peak to peak amplitudes showed a degree of variability dependent on the range of intensities. The lowest range showed stable amplitudes and slopes which were highly positive. Cortical responses increased to increasing intensity of stimuli. In the highest range cortical responsiveness often decreased (negative slopes) but the amplitudes were as variable within as between cats. In contrast the VEP amplitudes and slopes in the medium range of intensities were quite consistent, both between runs on the same day and between sessions a month apart. At this intensity range the VEP provided a stable and reliable electrophysiological measure of individual differences between cats. This study was reported in the second appended abstract (Saxton, Siegel & Lukas 1983).

4. Two final VEP sessions with the same group of cats further tested the stability of the VEP amplitude slopes at the medium versus high ranges of intensity. Additional computer programs for handling the data collection were developed, making possible a study of the effect of method of presentation. Four runs were presented at one intensity range during each session. In two runs blocks of 50 flashes in ascending order maximized the arousal effect of intensity increases, while in the other 2 runs blocks of 10 flashes were presented in semirandom order of intensities. The first 4 major components were analyzed as both baseline to peak and

peak to peak measures. It was found that the early components P1, N1 and P2 were most stable. The earliest component B-P1 showed little response to intensity in most cats, so that the peak to peak amplitude P1-N1 strongly correlated with baseline to N1 (B-N1). A manuscript in preparation presents the stability and reliability of the VEP over different ranges of intensity and with the two methods of presentation. (The Visual Evoked Potential as an Individual Signature in Cats. Saxton, Siegel & Lukas, in preparation).

5. These same cats were also subjected to behavioral tests, observing spontaneous behavior in the lab and in the behavioral chamber with the presentation of novel and stressful stimuli as described in the first study. The behavior of each cat was rated by two observers and videotaped for further analysis. Behavioral scales included visual contact, emotionality, exploration, aggression and withdrawal. Correlations of the medium intensity slopes with the behavioral ratings were most promising with initial exploration and activity in the chamber (0.31 to 0.62) and with approach to the novel/aversive stimuli (0.51). Augmenter cats were more active and exploratory and tended to investigate new and strange stimuli. The remaining correlations were erratic and nonsignificant. Although cat behavior in response to these stimuli does show individual differences, these are only weakly correlated with the electrophysiological differences.

6. A more direct behavioral measure of performance in a stressful task situation was then developed according to the following reasoning. If augmenting/reducing is based upon overall differences in inhibitory pathways in the brain then we would expect to find a correlation between the VEP measure of augmenting/reducing and a behavioral measure of inhibition. The same group of cats was trained to bar press for food reward on first a fixed interval and then a differential reinforcement of low rate of response (DRL) schedule. In each case there were two bars available, the correct one cued by a flashing light at the end of the intertrial interval. After the cat reached a steady level of performance in each situation, stress was introduced in the form of random, loud (95 dB) noise bursts. Following this in the DRL situation a variable of task difficulty was introduced by having lights flashing at different frequencies above each bar. The correct bar was always signalled by the training frequency (10/sec), while the frequency of the other light increased from 1/sec on the first day to 8/sec on the final day of testing. Measures

were taken of baseline levels of performance and time to learn for both fixed interval and DRL training, and the effect of noise and task difficulty upon performance. There were significant individual differences in learning and in response to the stressful situations. These measures were then correlated with the VEP augmenting/reducing. Augmenting/reducing, as measured by the most stable components of the VEP, P1-N1 and B-N1, correlated significantly with the time to learn the DRL task and with the overall rating of performance in the DRL situation such that reducers learned more quickly, were more efficient, made fewer extra presses when distracted by the noise and showed more inhibitory control. This was an unexpected finding since in the spontaneous behavioral reactions (see sections 1 and 5 above) augmenters were more responsive and reactive. Only in the task behavioral situation did it become apparent that reducers were able to control their behavior more readily while learning the task equally well. (Relationship between Visual Evoked Potentials and Operant Performance in Cats. Saxton, Siegel and Lukas, in preparation).

RAT STUDIES

Previous work in this lab showed that measurements of VEP amplitudes in Wistar rats restrained by towel wrapping showed augmenting/reducing of the primary components as well as the light flash-evoked afterdischarge (Como et al. 1979). Frontal lobe lesions differentially affected reducing of the VEP, leaving augmenters unchanged. The after discharge amplitude, optimally produced during low levels of reticular activation (Fleming et al. 1973; Schwartzbaum 1975), continued to decrease at high intensities of light stimulation for both augmenter and reducer rats. This study suggested that augmenting/reducing may be a function of frontal pole control of arousal level (Como et al. 1979, abstract appended).

The relationships among levels of activity, responsiveness, exploration and cortical arousal were assessed in the next series of experiments (Joseph et al. 1981; reprint appended). Inbred Wistar rats at 90 or 120 days of age were separated by their behavior in a complex environment (i.e. a closed field) into low active and high active individuals. High active subjects demonstrated significantly lower afterdischarge amplitudes. A second group of rats tested and retested after 45 days in the closed field showed that high or low behavioral responsiveness is a stable characteristic.

Subjects were then tested for preference for a familiar versus novel compartment. No differences were found between high and low active rats in preference, but the latency to move was significantly shorter for the high active rats. Further testing in a less complex open field showed no differences between rats. These findings showed that a high level of arousal as a response to a highly complex environment or intense stimulation is not related to generalized activity. They further indicated that similarly reared rats may be differentially influenced by novel, complex or intense stimuli, such that some subjects become highly responsive and cortically aroused, whereas others respond with low levels of behavioral and cortical activation.

These studies indicated that the rat, like the cat, can adequately serve as an animal model for the augmenting/reducing phenomenon. In order to decrease the possible effect upon the VEP due to restraint, a mirrored box was built (Dyer and Annau 1977) from which to record VEPs. Two behaviorally distinct strains of rats (Zivic-Miller and Fischer 344) were chosen on the basis of their differential response to an active avoidance test (Ray & Barrett 1975). Seven rats of each strain were implanted for VEP recording. The VEP amplitudes for these rats in the mirror box were variable and subsequent experiments have continued to study the sources of this variability. Position in the box and activity have been studied by comparing 1) the freely moving rat, 2) towel restrained rat facing each wall, and 3) anaesthetized (40 mg/kg Nembutal) rat facing each wall. These data are still being analyzed and results will be submitted when completed.

LIST OF MANUSCRIPTS SUBMITTED OR PUBLISHED UNDER ARO SPONSORSHIP DURING THIS PERIOD, INCLUDING JOURNAL REFERENCES:

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Saxton, P. M., Siegel, J. and Lukas, J. H. The Visual Evoked Potential as an Individual Signature in Cats. (Manuscript in preparation.)

Saxton, P. M., Siegel, J. and Lukas, J. H. Relationship Between Visual Evoked Potentials and Operant Performance in Cats. (Manuscript in preparation.)

*ATTACHED AS APPENDIX

SCIENTIFIC PERSONNEL SUPPORTED BY THIS PROJECT AND DEGREES/PROMOTIONS DURING THIS REPORTING PERIOD:

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